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Practitioner's Docket No. U 014724-2

**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of: MANNE SATYANARAYANA REDDY, et al.

Serial No.: 10/622,098

Group No.: 1614

Filed: July 17, 2003

Examiner:

For: FORMS OF DUTASTERIDE AND METHODS FOR PREPARATION THEREOF

**Commissioner for Patents**

**P. O. Box 1450**

**Alexandria, VA 22313-1450**

**TRANSMITTAL OF CERTIFIED COPY**

Attached please find the certified copy of the foreign application from which priority is claimed for this case:

Country: INDIA

Application  
Number: 534/MAS/2002

Filing Date: July 17, 2002

**WARNING:** "When a document that is required by statute to be certified must be filed, a copy, including a photocopy or facsimile transmission of the certification is not acceptable." 37 C.F.R. 1.4(f) (emphasis added).

**CERTIFICATE OF MAILING (37 C.F.R. 1.8a)**


I hereby certify that this correspondence is, on the date shown below, being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Date: December 4, 2003

  
Signature

**JANET I. CORD**

(type or print name of person certifying)



SIGNATURE OF PRACTITIONER

JANET I. CORD

(type or print name of practitioner)

Reg. No. 33,778

Tel. No.: (212) 708-1935

P.O. Address

Customer No.: 00140

c/o Ladas & Parry  
26 West 61<sup>st</sup> Street  
New York, N.Y. 10023

*NOTE: "The claim to priority need be in no special form and may be made by the attorney or agent, if the foreign application is referred to in the oath or declaration, as required by § 1.63." 37 C.F.R. 1.55(a).*

**THE PATENTS ACT, 1970**

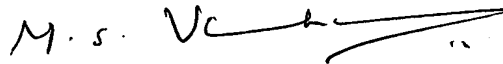
It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification, Complete Specification, Abstract & Drawings of the extract of Patent Application No.534/MAS/2002, dated 17.07.2002 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad 500 016, Andhra Pradesh, India.

.....


.....In witness thereof

I have hereunto set my hand

Dated this the 13<sup>th</sup> day of November 2003  
22<sup>nd</sup> day of Kartika, 1925(Saka)



(M.S. VENKATARAMAN)  
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

  
**PATENT OFFICE BRANCH**  
**GOVERNMENT OF INDIA**  
Guna Complex, 6<sup>th</sup> Floor, Annex.II  
No.443, Anna Salai, Teynampet, Chennai – 600 018

Received Rs 5000/- in Cash  
Cheque No. 101 P.O.D.D. on 17-07-02  
Vide C.B.A. No. 4340.

FORM 1

THE PATENTS ACT, 1970  
(39 of 1970)  
APPLICATION FOR GRANT OF A PATENT  
(Section 5(2), 7, 54 and 135 and Rule 33A)

1. ☒ We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016
2. hereby declare -
  - (a) that I-am/ we are in possession of an invention titled "**Novel crystalline polymorphic forms of Dutasteride and process for preparation thereof**"
  - (b) that the Provisional/Complete specification relating to this invention is filed with this application.
  - (c) that there is no lawful ground of objection to the grant of a patent to me/us.
3. further declare that the inventor(s) for the said invention is/are **Manne Satyanarayana Reddy, Chakilam Nagaraju, Gudipati Srinivasulu Mandava Venkata Naga Brahmeshwar Rao and Bojja Ram chandra Reddy**. All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh**.
4. ☒ We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.
5. ☒ We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/patantee
6. ☒ We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on \_\_\_\_\_ under section 16 of the Act.
7. That I-am/We are the assignee or legal representative of the true and first inventors.
8. That my/our address for service in India is as follows:


Dr. Manne Satyanarayana Reddy  
Vice-President-R&D  
Dr. Reddy's Laboratories Limited  
7-1-27, Ameerpet  
Hyderabad, A.P., 500 016  
Phone: 040- 3095578  
Fax: 040-3095438

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17 JUL 2002 534 IAS 2002

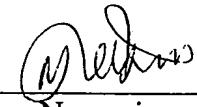
9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:

~~I/We~~, the true and first inventors for this invention or ~~the applicant(s)~~ in the convention country declare that the applicant(s) herein ~~is/are my/our~~ assignee or legal representative

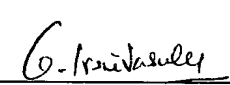
(Signed) \_\_\_\_\_

  
Manne Satyanarayana Reddy,  
H.No. 8-3-167/D/16,  
Kalyan Nagar,  
Near AG Colony,  
Erragadda,  
Hyderabad-500 038.

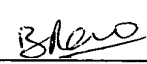
(Signed) \_\_\_\_\_

  
Chakilam Nagaraju,  
12-10-336/15/1,  
Seethaphal Mandi,  
Secunderabad – 500 061.

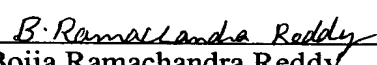
(Signed) \_\_\_\_\_

  
Gudipati Srinivasulu,  
15-21-107,  
Balajinagar,  
Kukatpally,  
Hyderabad – 500 072.

(Signed) \_\_\_\_\_

  
Mandava Venkata Naga Brahmeshwar Rao,  
H.No. 1-76,  
Near BJP Office,  
Kukatpally,  
Hyderabad – 500 072.

(Signed) \_\_\_\_\_

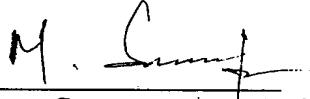
  
Bojja Ramachandra Reddy  
EWS - 248, III line  
KPHB Colony  
kukatpally,  
Hyderabad. - 500072

10. That to the best of ~~my~~/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to ~~me~~/us on this application.
11. Following are the attachments with the application
- (a) Provisional/~~Complete~~ specification (~~---~~<sup>0.5</sup> pages, in triplicate)
  - (b) Drawings (~~---~~<sup>0.2</sup> pages, in triplicate)
  - (c) Priority documents(s)
  - (d) Statement and Undertaking on Form-3.
  - (e) Power of authority
  - (f) Abstract of the invention (----- page, in triplicate)
  - (g) Fee Rs. 5000.00 (five thousand rupees only) in Cash/cheque/bank draft bearing No. 336203 dated 04.07.2002 drawn on HDFC Bank Limited, Lakdikapool, Hyderabad - 4.

I/We request that a patent may be granted to me/us for the said invention.

Dated this 26<sup>th</sup> day of July 2002.

To,  
The Controller of Patents  
The Patents Office Branch, Chennai.

(Signed)   
Dr. Manne Satyanarayana Reddy  
Vice-President (R&D)  
Dr. Reddy's Laboratories Limited.

**FORM 2**

**THE PATENTS ACT, 1970**

**PROVISIONAL SPECIFICATION**

**(SECTION 10)**

**Novel Crystalline Polymorphic forms of Dutasteride and Process for  
preparation thereof**

**Dr. Reddy's Laboratories Ltd.**

**an Indian Company having its registered office at**

**7-1-27, Ameerpet**

**Hyderabad – 500 016, A.P., India**

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

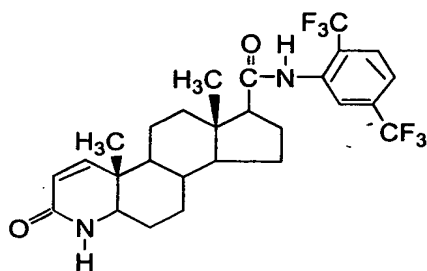
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**Field of the Invention:**

The present invention relates to novel crystalline polymorphic forms of Dutasteride, which is chemically known as 17 $\beta$ -N-[2,5-bis (Trifluoromethyl)phenyl]carbamoyl-4-aza-5 $\alpha$ -androst-1-en-3-one and shown as Formula (I). The present invention also relates to process for preparing the novel crystalline polymorphic forms of Dutasteride.



Formula (I)

Dutasteride is useful in the treatment of androgen responsive and mediated diseases.

**Background of the invention:**

US Patent 5,565,467 claimed Dutasteride and its related compounds. It also claimed the pharmaceutical formulations thereof and their use in the treatment of androgen and mediated diseases.

The '467 patent discloses a process for the preparation of Dutasteride, which comprises the condensation of 17 $\beta$ -N-(2,5-bis (Trifluoromethyl) phenyl) carbamoyl-4-aza-5 $\alpha$ -androstane-3-one, 2,3 -dichloro-5, 6-dicyano-1, 4-benzoquinone and bis(tri methylsilyl)trifluoroacetamide in dioxane as solvent and the resultant solid is crystallized from a mixture of ethyl acetate - heptane in a ratio of 1:1 v/v.

No relevant references of Dutasteride were disclosed the crystalline Polymorphic forms till date.

Polymorphism can be defined as the ability of the same chemical substance to exist in different crystalline structures. The different structures are referred to as polymorphs, polymorphic modification or form.

Hence, the first object of the present invention is to provide the novel crystalline forms of Dutasteride.

The second object of the present invention is to prepare the novel crystalline forms of Dutasteride. The crystalline forms of Dutasteride of present invention are designated as Form-I and Form-II for convenience.

The crystalline forms of the present invention are characterized by X-ray diffractogram pattern. The XRD patterns are well distinguished to each other indicating the difference in the crystalline structure.

The novel crystalline forms of Dutasteride may be well suited for pharmaceutical formulations and can be used in the treatment of androgen and mediated diseases.

**Brief description of accompanying drawings:**

Fig-1: X-Ray powder diffractogram of Dutasteride Form-I.

Fig -2: X-Ray powder diffractogram of Dutasteride Form-II.

**Summary of the invention:**

The present invention provides novel crystalline forms of Dutasteride and process for preparation thereof. The novel crystalline forms of present invention are designated as Form-I and Form-II. The crystalline Form-I and Form-II of Dutasteride are characterized by X-ray diffractogram pattern. The process for the preparation of these crystalline forms

comprises the dissolution of Dutasteride in polar organic solvents accompanied by distillation of the solvent and further isolation by adding an organic solvent, preferably less polar than initial solvent to afford the novel crystalline forms.

**Detailed description of the invention:**

The present invention provides the novel crystalline Form-I and Form-II of Dutasteride and process for their preparation.

The crystalline Form-I and Form-II of Dutasteride of present invention is characterized by X-ray diffractogram, which are measured on Bruker Axe, DS Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

The process for the preparation of novel crystalline Form-I of Dutasteride comprises:

- (i) dissolving the crude Dutasteride in haloalkane solvents, preferably dichloromethane;
- (ii) distilling the solvent from the reaction solution;
- (iii) adding the non-polar organic solvent such as cyclohexane to the resultant residue obtained in step (ii);
- (iv) filtering the crystallized solid accompanied by drying the compound in conventional methods to afford the novel crystalline Form-I of Dutasteride.

The crystalline Form-I of Dutasteride obtained in the above process is characterized by the X-ray powder diffraction pattern. The d-spacings (in  $\text{\AA}$ ) of the identified peaks in the X-ray diffractogram are 16.85, 8.59, 7.44, 6.93, 6.29, 5.95, 5.63, 5.58, 5.32, 4.98, 4.78, 4.49, 4.32, 4.10, 4.04, 3.86, 3.75, 3.59, 3.46, 3.30, 3.17, 2.95, 2.75, 2.65, 2.39 and 2.23.

The process for the preparation of novel crystalline Form-II of Dutasteride comprises:

- (i) dissolving the crude Dutasteride in alcoholic solvents having C<sub>1</sub>-C<sub>5</sub> carbon atoms, preferably methanol;
- (ii) distilling the solvent from the reaction solution;
- (iii) adding ester solvents such as ethyl acetates to the resultant residue obtained in step (ii);
- (iv) filtering the crystallized solid accompanied by drying the compound in conventional methods to afford the novel crystalline Form-II of Dutasteride.

The crystalline Form-II of Dutasteride obtained in the above process is characterized by the X-ray powder diffraction pattern. The d-spacings (in Å) of the identified peaks in the X-ray diffractogram are 13.37, 12.23, 11.53, 10.13, 9.42, 8.61, 8.31, 7.95, 7.38, 6.91, 5.85, 5.73, 5.62, 5.11, 4.92, 4.76, 4.69, 4.56, 4.45, 4.28, 4.07, 3.98, 3.81, 3.45, 3.29, 3.17, 3.15, 3.11, 2.92, 2.48, 2.29 and 2.16.

Dated: 16<sup>th</sup> day of July 2002.

Signed)



Dr. Manne Satyanarayana Reddy,  
Vice-President (R&D),  
Dr. Reddy's Laboratories Limited.

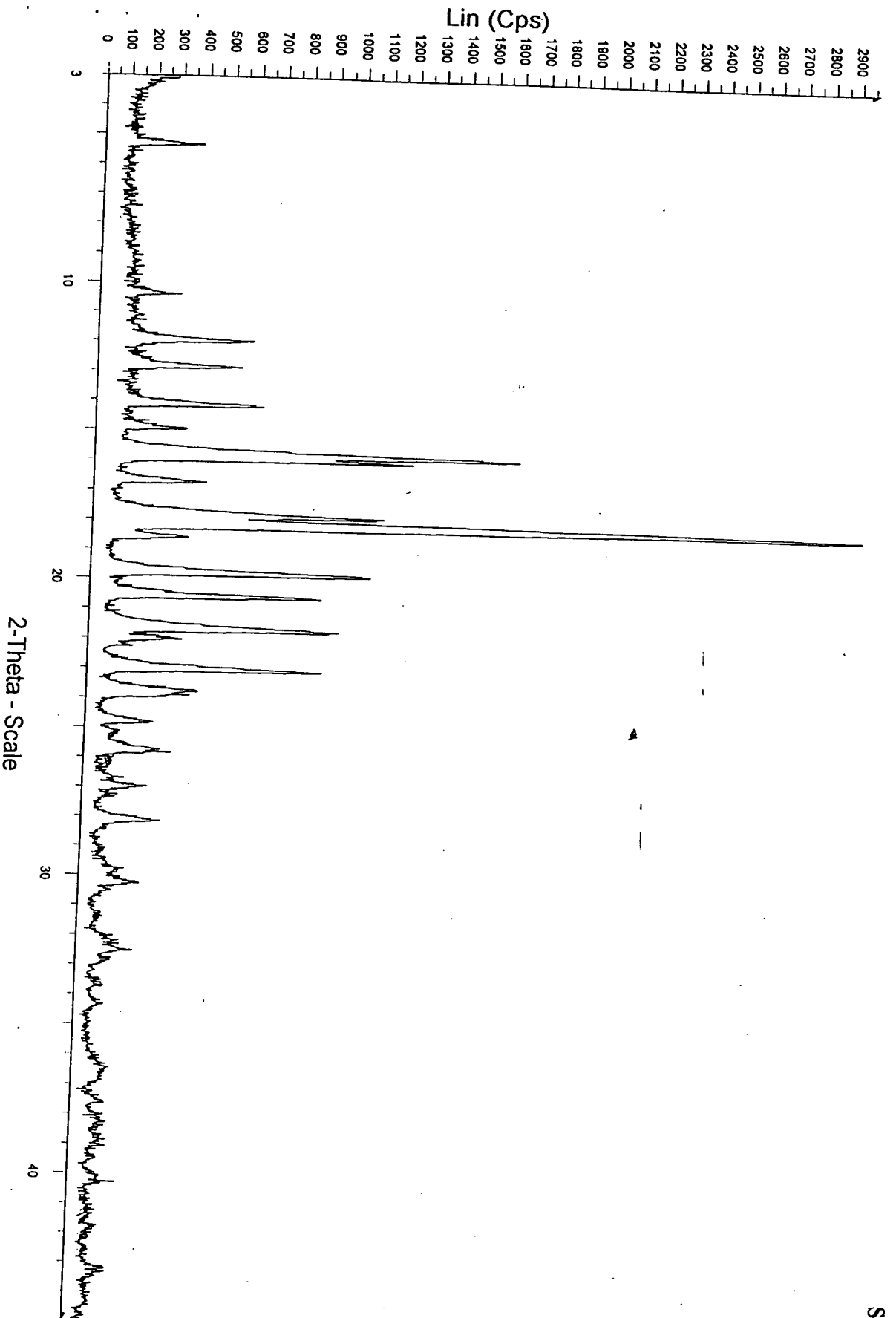


Fig. (1)

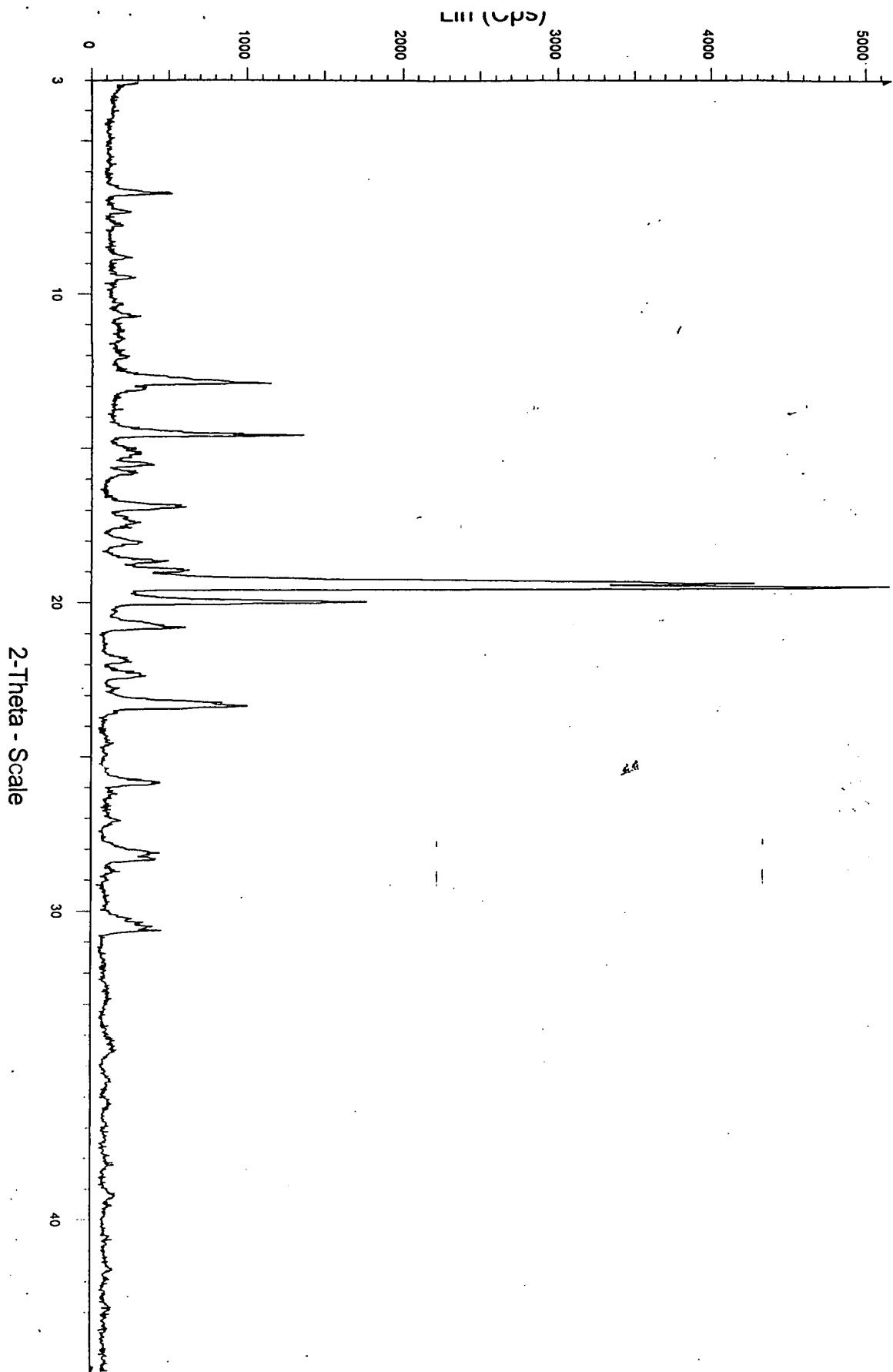


Fig. (2)